UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/689,866	10/21/2003	Benjamin Oshlack	200.1133CON	3333

7590 07/22/2009

DAVIDSON, DAVIDSON & KAPPEL, LLC
14th Floor
485 Seventh Avenue
New York, NY 10018

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
07/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/689,866	OSHLACK ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59 and 61-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-59 and 61-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/09;6/15/09;6/17/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Response after Non-Final Office Action, the Amendment and Applicant's Arguments/Remarks, all filed 04/13/09 is acknowledged. The Information Disclosure Statements (IDS) filed 02/24/09, 06/15/09 and 06/17/09 are also acknowledged.

Applicant has overcome the following objection and/or rejection by virtue of the amendment to the claims and/or persuasive remarks: (1) The claim objection for claims 62-63 has been withdrawn; (2) The 35 U.S.C. §103(a) rejection over Palermo (WO 99/32120) has been withdrawn.

Claims 1-59 and 61-73 are pending in this action. Claims 1-9, 41 and 54 have been amended. New claims 65-73 have been added. Claim 60 has previously been cancelled. Claims 1-59 and 61-73 remain rejected.

* * * * *

Claim Objections

Claim 66 is objected to because of the following informalities:

Claim 66 contains a typographical error. The term "is" has been provided in duplicate.

Appropriate correction is required.

* * * * *

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 41 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim limitation "wherein an amount of the antagonist released from the dosage form which has been administered intact is insufficient to produce a physiological effect of the antagonist in a human patient" introduces new matter into the claims. The Applicant directs the Examiner to page 5, lines 8-12, page 14, lines 5-6 and pages 64-66 for support for the claimed limitation. However, the Examiner fails to find sufficient support in the specification for this newly added limitation, based on the pages/lines identified by Applicant. There is no mention of "the antagonist that is released from the dosage form which has been administered intact is insufficient to produce a physiological effect of the antagonist". The specification is silent as to any mention or reference to physiological effects that can or cannot be produced. Thus, the limitation as now presented by Applicant has not been amply supported.

* * * * *

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-59 and 61-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaiko *et al.* (hereinafter "Kaiko") (U.S. Pat. No. 6,277,384).

Kaiko ('384) teaches oral dosage forms comprising a combination of an orally analgesically effective amount of an opioid agonist and an orally active opioid antagonist, the

opioid antagonist being included in a ratio to the opioid agonist to provide a combination product which is analgesically effective when the combination is administered orally, but which is aversive in a physically dependent subject (see Abstract); (col. 5, lines 1-18). Kaiko also teaches a method of treating pain comprising the opioid agonist (analgesic) which reducing the abuse potential of the dosage form (column 4, lines 46-67). The method for treatment comprises orally administering an orally analgesically effective amount of an opioid agonist together with an opioid antagonist in a ratio which maintains analgesic efficacy by the opioid analgesic but which may decrease analgesia somewhat by direct measurement in patients or by the use of one or more surrogate measures of opioid effect in human subjects (col. 5, lines 58-64).

Suitable opioid agonists taught include hydrocodone (col. 5, lines 33-37). Additional analgesics are taught at column 11, lines 34-65. Suitable antagonists disclosed include for example, naltrexone (col. 5, lines 33-37). Other antagonists disclosed include naloxone, nalmephene, cyclazocine and levallorphan (col. 10, lines 3-29).

The pharmaceutical compositions may be in the form of tablets, multiparticulate formulations, powders, granules, matrix spheroids or coated inert beads and the like (col. 7, lines 18-27). The dosage forms may provide an immediate release of the opioid agonist and opioid antagonist. In certain embodiments, the dosage forms provide a sustained release of the opioid agonist, and provide the part or all of the dose of the opioid antagonist in (i) immediate release form; (ii) sustained release form or (iii) both immediate release and sustained release form. Sustained release may be accomplished, e.g., via a sustained release carrier into a matrix containing the opioid agonist and opioid antagonist or via a sustained release coating of a matrix

containing the opioid agonist and opioid antagonist (col. 7, lines 27-42). In some embodiments, a combination of two opioid analgesics can be included (col. 7, lines 59-60).

In preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (col. 17, lines 28-54). For instance, the hydrophobic material can be used to coat inert pharmaceutical beads such as non-pareil beads (col. 19, lines 45-53). Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, non-pareil beads. The resultant coated substrate (i.e., beads) may then be optionally overcoated with a barrier agent to separate the therapeutically active agent from the hydrophobic controlled release coating. The beads may then be overcoated with an aqueous dispersion of the hydrophobic material (col. 20, lines 1-29). A combination of two or more hydrophobic materials can be used (col. 22, lines 56-62). This teaching meets Applicant's requirement of the sequestering material comprising, for example, a cellulose polymer or an acrylic polymer, as in instant claims 24-26.

Suitable and preferred alkylcellulose polymers taught include ethylcellulose (col. 17, lines 46-54). Acrylic polymers are also disclosed and include acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid) and the like (col. 18, line 9 – col. 19, line 23). Plasticizers can also be included in the composition col. 19, lines 24-41). A process for preparing coated beads is disclosed at column 19, lines 46-67. Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials and any

pharmaceutically acceptable hydrophobic material or hydrophilic material, which is capable of imparting, controlled release of the active agent and which melts (or softens to the extent necessary to be extruded) may be used in this invention (col. 21, lines 50-57).

Kaiko teaches that the abuse potential of opioid analgesics is surprisingly curtailed by their invention. It is possible to combine in a single oral dosage form an opioid analgesic together with a small amount of opioid antagonist to achieve a product which still provides analgesia but which substantially negates the possibility that a physically dependent human subject will continue to abuse the drug by taking more than one tablet at a time, e.g., 2-3 times more than the usually prescribed dose (col. 13, lines 37-61).

With regards to amounts of hydrophobic material claimed, the Examiner notes that suitable or effective amounts can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters attainable within the art. Moreover, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Furthermore, Kaiko teaches that their controlled release profile can be altered, for example, by varying the amount of overcoating with the hydrophobic material (col. 19, lines 54-67).

Regarding the claim limitation of "a sequestering material separating the opioid antagonist from the opioid agonist" as recited, for example, in instant claims 1-7 (and additional claims), it is noted that Kaiko does teach the use of an overcoating with a barrier agent, for

instance, to separate the therapeutically active agent from the hydrophobic controlled release coating. The beads may then be overcoated with an aqueous dispersion of the hydrophobic material (col. 20, lines 1-29). While Kaiko does not indicate that their hydrophobic material/coating (i.e., sequestering material) is provided in a way so as to separate the antagonist from the opioid agonist, it is the position of the Examiner that the prior art does not have to teach this property (separation of agonist from antagonist), but merely that the prior art suggest using the material (hydrophobic material) for any reason. In this instance, since the art does clearly suggest use of the same hydrophobic coating materials (i.e., Applicant's sequestering material) used in the same field of endeavor as the Applicant, burden would be shifted to Applicant to show that the hydrophobic coating materials disclosed by the prior art would not be suitable for their intended function.

With respect to claims pertaining to the effects produced by the opioid antagonist, such as when the dosage is intact or alternatively, tampered with, Kaiko sufficiently meets these limitations. Kaiko teaches that their dosage forms resist abuse potential and can provide an aversive experience when a large amount of the combination product, e.g., about 2-3 times the usual prescribed dose, is taken by or administered to a physically dependent subject. Furthermore, the use of opioid antagonists (i.e., naltrexone) are known to prevent euphorigenic effects of the opioid agonists and also provide a blocking action. Even further, Kaiko discloses that their invention is directed in part to the surprising finding that there exists a ratio of opioid antagonist to opioid agonist (analgesic) which is analgesically effective when the combination is administered orally, but which is aversive to a physically dependent subject (col. 5, lines 4-33). These teachings read on Applicant's limitation of "the antagonist released from a dosage form

which is intact, is insufficient to produce a physiological effect of the antagonist in a human patient" as now recited by Applicant.

Pertaining to instant claim 64 which presents particular release rates of the antagonist, when the antagonist is intact, Kaiko teaches suitable weight ratios for the opioid agonist:antagonist components but does not explicitly teach Applicant's release rates. However, it is the position of the Examiner that the determination of effective or suitable release profiles is within the level of one of ordinary skill in the art through routine experimentation to obtain optimal results, since these are variable parameters attainable within the art.

With regards to the recitation of an opioid antagonist that is "sequestered", the term "sequestered", even as defined by Applicant's specification, merely requires that the formulation at some point in time be non-releasable (see specification, page 5, lines 23-31). The formulations containing opioid antagonists as disclosed by Kaiko would function in the same manner as instantly desired, such as in blocking or reversing the effects of the opioid agonists to avoid or resist misuse and abuse. Hence, no distinction has been observed that would result in a *patentable* distinction based on the instant antagonist versus those (antagonists) disclosed by the art.

The Kaiko reference explicitly recognizes and teaches oral dosage forms comprising opioid agonists in combination with opioid antagonists, whereby the dosage forms are effective for the substantial reduction of pain.

Regarding new claims 65-73, the limitations are met by the teachings of Kaiko. Kaiko discloses that their composition is analgesically effective when the combination is administered orally, but which is aversive to a physically dependent subject, for example a subject who

consumes more than 2-3 times the usual prescribed dose of opioid agonist (col. 5, lines 4-33). This meets the limitations of claims 65-69. Regarding claims 70-73, Kaiko teaches that the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (col. 17, lines 28-54). A combination of two or more hydrophobic materials can be used (col. 22, lines 56-62). Suitable acrylic polymers are disclosed at col. 18, line 9 – col. 19, line 23. This teaching meets Applicant's requirement of the sequestering material being for example, an acrylic polymer, as in instant claims 70-73.

Hence, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Response to Arguments

Applicant's arguments filed 04/13/09 have been fully considered and were found to be partially persuasive.

- **Claim Objections:**

Applicant argued, "The Examiner stated that the claims should recite 'any one of' rather than 'any of'. Claims 62-63 have been amended in accordance with the Examiner's suggestions."

Applicant's arguments were persuasive based on the amendment to the claims. Accordingly, the claim objection for claims 62-63 has been withdrawn.

- **Rejection under 35 U.S.C. §103(a) over Palermo (WO 99/32120):**

Applicant argued, "The Palermo Publication does not teach or suggest particles of the opioid antagonist which are free from the opioid agonist, because Palermo teaches to combine an opioid agonist with an opioid antagonist such that at least a two-step extraction process would be required to separate the opioid antagonist from the opioid agonist. The particles of Palermo would therefore necessarily have both an opioid antagonist and opioid agonist."

Applicant's arguments have been fully considered and were deemed persuasive by virtue of the amendment to the claims which presents "consisting of" language. Accordingly, the 35 U.S.C. §103(a) rejection over Palermo (WO 99/32120) has been withdrawn.

- **Rejection under 35 U.S.C. §103(a) over Kaiko (USPN 6,277,384):**

Applicant argued, "The Kaiko reference describes dosage forms which produce a physiological effect of the opioid antagonist in a human patient (i.e., "at least a mildly negative, "aversive" experience in physically dependent addicts"). *See, e.g., Abstract.* The Kaiko reference does not provide a reason for one skilled in the art to formulate an oral dosage form releasing an amount of the antagonist which "is insufficient to produce a physiological effect of the antagonist in a human patient" upon oral administration of the intact dosage form as recited in independent claims 1-9, 41 and 54."

Applicant's argument has been considered but was not persuasive. With respect to claims pertaining to the effects produced by the opioid antagonist, such as when the dosage is intact or alternatively, tampered with, Kaiko sufficiently meets these limitations. Kaiko teaches that their dosage forms resist abuse potential and can provide an aversive experience when a

large amount of the combination product, e.g., about 2-3 times the usual prescribed dose, is taken by or administered to a physically dependent subject. Furthermore, the use of opioid antagonists (i.e., naltrexone) are known to prevent euphorigenic effects of the opioid agonists and also provide a blocking action. See column 4, lines 46-67. The product of Kaiko provides sufficient analgesic properties and substantially negates the potential that a physically dependent human subject will continue to abuse the drug (such as by taking more than one tablet at a time, e.g., 2-3 times more than the usual prescribed dose). See column 13, lines 37-61. Furthermore, Kaiko discloses that their invention is directed in part to the surprising finding that there exists a ratio of opioid antagonist to opioid agonist (analgesic) which is analgesically effective when the combination is administered orally, but which is aversive to a physically dependent subject (col. 5, lines 4-33). These teachings read on Applicant's limitation of "the antagonist released from a dosage form which is intact, is insufficient to produce a physiological effect of the antagonist in a human patient" as now recited by Applicant. Furthermore, as noted above, ample support has not been established for this claim limitation as now presented, and thus constitutes new matter under 35 U.S.C. §112, 1st paragraph.

Next, Applicant argued, "The Kaiko reference also does not provide a reason for one skilled in the art to formulate an oral dosage from providing the specific degrees of sequestration as recited in claims 1-7. The Kaiko reference is not concerned with the sequestration of the opioid antagonist as recited in independent claims 1-9, 41 and 54."

This argument was not found convincing. This argument was not persuasive since the degree of sequestration argued by Applicant does not demonstrate that the instant invention would be materially different than the compositions of the art, which teaches use of the same

components, such as the hydrophobic coatings (i.e., sequestering material) in a similar manner to yield similar effects and results and treats the same problems (i.e., pain) as that desired by Applicant. The prior art clearly suggests use of the same hydrophobic coating materials and burden would be shifted to Applicant to show that the hydrophobic coating materials disclosed by the prior art would not be suitable for their intended function. Moreover, any difference in sequestration levels would be only a difference in degree and not of kind.

Applicant argued, "With further regard to claim 64, Applicants submit that the Kaiko reference does not suggest "an amount of the antagonist released from the dosage form which has been administered intact [that] is less than an amount bioequivalent to 0.125 mg of naltrexone" as recited in claim 64."

Pertaining to instant claim 64 which presents particular release rates of the antagonist, when the antagonist is intact, Kaiko teaches suitable weight ratios for the opioid agonist:antagonist components but does not explicitly teach Applicant's release rates. However, it remains the position of the Examiner that the determination of effective release profiles is within the level of one of ordinary skill in the art obtained via routine experimentation to achieve optimal results, since these are variable parameters attainable within the art.

This rejection has been maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/

Primary Examiner, Art Unit 1615

hns

July 16, 2009